11. Mergers and alliances in pharmaceuticals: effects on innovation and R&D productivity

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I INTRODUCTION

The pharmaceutical industry provides a good laboratory to investigate the effects of mergers and alliances on innovation and R&D productivity. Over the past few decades, the industry has been characterized both by significant consolidation of large pharma firms as well as the vertical disintegration of the R&D process. The latter is associated with significant entry into the discovery and development process by early stage biopharmaceutical firms. Since the early 1990s, an evolving marketplace for new technologies through licensing agreements and joint ventures has emerged, accompanied by the growth of contract research organizations that specialize in implementing clinical trials for new drug candidates.

To put some of these changes in historical perspective, it is useful to chronicle some of the key dynamic forces affecting the pharmaceutical industry since the early 1980s. While the 1980s were a period of rising prices and profits for the industry, many challenging developments also occurred for the vertically integrated, multinational drug industry. These developments included rising R&D costs (DiMasi et al., 1991; 2003), the expiration of patents on major commercial products, and the beginning of intensive price competition from generics. The passage of the Waxman–Hatch Act in 1984 was a key legislative change that allowed generics to enter the market by demonstrating bioequivalence (that is without the need to do clinical tests of safety and efficacy) (Grabowski, 2007). These dynamic forces intensified in the 1990s with the rise of buyer-side market power in the form of managed care organizations and pharmacy benefit managers in the US, and increasingly stringent price controls in other major world markets. Market and political pressures have caused declining growth in sales and profits that have been particularly evident on an industry-wide basis since the mid-1990s.
There has been increasing attention over recent years to whether the pharmaceutical industry is now in an R&D productivity crisis. Several observers have pointed to a pattern of rising R&D expenditures accompanied by a declining trend in new molecular entities since the mid-1990s. The productivity crisis idea is subject to various qualifications relating to the quality of NMEs, the long lags that characterize the R&D process in pharmaceuticals, and a gradual shift to a new R&D paradigm based more on biology than chemistry (Cockburn, 2006). Nevertheless, the declining trend in new products from the R&D labs, along with continuing patent expirations on prior ‘blockbuster’ products has created a replacement problem for many large pharma firms.

The structural response to these dynamic forces has included both large horizontal mergers as well as a growing number of development-stage agreements between large pharma firms and smaller, research-based biopharmaceutical firms. The first merger wave began in the 1989–1990 period. The annual value of pharmaceutical mergers in these two years exceeded that of any prior year in the 1980s by a considerable margin (Ravenscraft and Long, 2000). This was followed by an even larger merger wave beginning in the mid-1990s and continuing into the 2000s (Danzon et al., 2007; Koenig and Mezick, 2004). Combinations have included not only mergers between large pharma firms but also the acquisitions of biotech firms by pharma firms and mergers between firms of different sizes in the emerging biotech sector.

Table 11.1 shows how the global market shares in the pharmaceutical firms have changed between 1989 and 2004. All the blocked companies consummated a major merger in the period between the prior rankings shown in Table 11.1. Correspondingly, the starred companies were combined into larger entities in the period between rankings. If one looks across the full 15-year span between 1989 and 2004, eight of the top ten ranked companies by 2004 had consummated major mergers with other biopharmaceutical firms (Merck and J&J being the notable exceptions). There were also many smaller scale mergers and acquisitions over this period.

Global shares for top ten firms increased to 48.3 per cent by 2004, compared to 28.3 per cent in 1989. Despite the increased merger activity, the pharmaceutical industry is still relatively unconcentrated compared to many other industry sectors. Many changes in company rankings also occur over time as a result of both new product introductions and patent expirations. This is reflected by the rapid growth of dedicated biotech firms like Amgen and also of primarily generic firms like Teva. These firms were part of the top 20 biopharmaceutical firms in 2004.

While mergers and acquisitions (M&A) have tended to occur in waves, there has been continued growth in the number and value of alliances.
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Source: IMS Health Care Market Share Data, based on merger histories compiled by Jon Northrop in Burns et al. (2005) p. 228.
between biopharmaceutical firms over time. Alliances can be a substitute for mergers and acquisitions, but can also be a forerunner to a future merger or acquisition between partners. A prototypical development stage agreement would involve payments of milestones and/or royalties and some sharing of R&D expenses in the exchange for rights to develop and/or market the new products covered under the agreement. The extent of integration at the R&D stage associated with these agreements varies considerably, ranging from true joint development agreements, to transfers of development stage products from licensors to licensees, to marketing options in exchange for development stage funding and future payments.

Figure 11.1 shows the number and potential value (including upfront payments, milestones and equity investments) of out-licensing deals from the biotech sector between 1997 and 2006. The number of annual out-licensing deals has more than doubled over this period, while the potential value has grown several fold (Recombinant Capital, 2007). The rapid growth in potential value in recent years reflects the fact that many deals are now frequently broader in scope than a single compound or a related family of compounds. It also reflects increasing potential values for licensors associated with the intense competition for deals in hot therapeutic areas like oncology (Ernst and Young, 2007).

In this chapter, our primary focus is on the effect of mergers and acquisitions on innovation and R&D productivity. However, since alliances can be either a substitute or longer-term complement to mergers, we also consider the empirical literature on the effects of alliances on these output measures. In the next section of the chapter we consider the motives for pharmaceutical
The following section summarizes evidence concerning the effects of mergers and alliances on R&D productivity and innovation. Section IV presents some preliminary findings from our own study on mergers using a large database of public and private firms and detailed data on clinical development outcomes over the 1990 to 2007 period. The final section provides some concluding observations and interesting questions for future research.

II DETERMINANTS OF MERGERS, ACQUISITIONS AND ALLIANCES

The motives for merger and acquisitions activity can be broadly categorized into adaptive or defensive rationales, versus proactive or offensive ones (Burns et al., 2005). In this section, we utilize this classification to consider the economic drivers of mergers and acquisitions in the pharmaceutical industry. It is important to understand the rationales for mergers before attempting to evaluate studies that are focused on the effects of mergers. We also consider the role of alliances as a substitute or complement to M&A activity.

A Defensive Motives: Strategic Response to Environmental Change

The hypothesis that industry-wide shocks can precipitate merger waves appears to be a useful concept in understanding pharmaceutical mergers. The original hypothesis goes back to Michael Gort (1969). Industry-wide shocks appear to explain merger waves in other industries such as banking and telecommunications in the 1990s (Andrade et al., 2001). In the case of pharmaceuticals, the economic environment became more difficult and pipeline gaps emerged throughout the industry by the late 1980s. With stock prices under pressure, many affected drug firms were motivated to use their accumulated cash flows to acquire another firm’s products and pipeline. The bidder could often pay the premium associated with these acquisitions by consolidating operations and cutting out the excessive infrastructure capacity. Various researchers have made the point that mergers and acquisitions facilitate disruptive organizational change that would otherwise meet with substantial internal inertia and resistance (Ravenscraft and Long, 2000). However, mergers are also associated with substantial integration costs that can affect the productivity of the firm in the post-merger period (Clark, 2001; Larsson and Finkelstein, 1999).

Ravenscraft and Long (2000) performed one of the first analyses of pharmaceutical mergers. Their analysis covered mergers of significant
value undertaken between 1985 and 1996. Using event studies, Ravenscraft and Long found that the large horizontal mergers and cross-border mergers created gains in overall stock market value. As in other industry studies, however, target firms captured most of the returns. Their findings are consistent with the response to the industry shocks, excessive capacity hypothesis. Their analysis of cost cutting for large horizontal pharmaceutical mergers found a reduction in total headcount in the post-merger period ranging from 8 per cent to 20 per cent of the combined workforce in the pre-merger period. While cost-cutting in manufacturing and marketing personnel was proportionately greater than for R&D employees, there was also a consolidation of R&D laboratories and the elimination of marginal R&D projects by several firms.

A subsequent analysis by CenterWatch of 11 large mergers (22 pharmaceutical companies) that occurred between 1989 and 1998 reported a 34 per cent average reduction in development projects three years after the merger was consummated (CenterWatch, 2000). Neither the Centerwatch study nor Ravenscraft and Long’s analysis, however, examined subsequent effects on the firms’ R&D productivity or the probability of success. To the extent that these reductions in R&D activities eliminated duplicate efforts or projects with low probability of success, or facilitated more external alliances, the companies’ R&D performance could have increased in the post-merger period compared to the pre-merger one. This issue is considered further below.

Other researchers also find evidence that firms under economic stress are more likely to engage in mergers. An often cited firm-specific motivation for pharmaceutical mergers and acquisitions (M&A) is to fill in gaps in a company’s pipeline to maintain growth in the face of a major product’s patent expirations. Patent expirations on major projects can produce rapid losses in unit sales to generic entrants and leave firms with substantial excess capacity in their marketing and sales forces. Pharmaceutical products exhibit a highly skewed distribution of revenues and returns (Grabowski et al., 2002).

Two recent analyses have found that pipeline gaps and issues continue to be a key driver of merger activity. A study of 202 biotechnology and pharmaceutical mergers between 1998 and 2001 found that pharmaceutical firms that have a relatively old portfolio of marketed drugs exhibit a higher propensity to acquire another firm (Danzon et al., 2007). A second study of 160 pharmaceutical mergers between 1994 and 2001 found that firms with lower scores in the strength of their R&D pipeline and fewer years of exclusivity on their marketed drugs had a greater probability of engaging in a merger (Higgins and Rodriguez, 2006).

The fact that firms in economic stress are more likely to engage in mergers creates methodological issues in evaluating pharmaceutical merger

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activity. In particular, one can not simply compare merging entities to overall industry performance. Rather, it is important to construct control groups with similar firm characteristics in evaluating the effects of a merger. This issue is considered further below.

B Economies of Scale and Scope and Other Proactive Rationales for Mergers

Proactive motives for mergers include increases in size to achieve critical mass and economies of scale in R&D and other firm activities. Firms may also engage in mergers to increase the number of therapeutic areas in their R&D programs in order to take advantage of economies to scope. Furthermore, firms may undertake mergers and acquisitions to bring new technologies and research tools into the firm to enhance their research productivity. Mergers may also reflect management goals to increase firm size and growth rates, even if this is not associated with increased profitability or productivity (Mueller, 1986).

A series of papers by Cockburn and Henderson (Cockburn and Henderson, 2001; Henderson and Cockburn, 1996) focusing on economies of scale and scope in drug R&D provide some insight on the effects of increased size on R&D productivity. They looked for the effect of scale and scope on productivity at a research program level, for ten large firms. The advantage of these papers is that they use extremely detailed data (including program-level R&D spending) over a very long time period. They conclude that firms engaged in a broader scope of research activities are more productive than focused firms, but that scale doesn’t matter much once the scope is controlled for. A recent paper by Danzon et al. (2005) finds benefits from a company’s development experience as measured by the number of drugs in clinical trials, but these benefits are also subject to diminishing returns. This study is discussed further in terms of the effects of alliances on R&D productivity.

The consolidation of the larger pharmaceutical firms shown in Table 11.1 has been accompanied by increasing breadth in the R&D activities of the leading firms in the industry across therapeutic categories. For example, Pfizer, as a result of its large-scale mergers with Warner Lambert and Pharmacia, now has R&D programs in new fields such as oncology, endocrinology and ophthalmology. This complements the company’s historical strengths in cardiovascular, depression, anti-infectives and erectile dysfunction (Burns et al., 2005). This increased breadth may produce economies of scope benefits over time as described in the academic literature by Cockburn and Henderson. However, Pfizer, along with some of the other leading pharmaceutical firms, now have annual R&D budgets of over
$5 billion to manage. At this size, companies may have entered a region of diminishing returns from the standpoint of managing and motivating creative individuals and coordinating their activities. It is notable that Pfizer, GlaxoSmithKline, and other firms with multi-billion dollar R&D programs and several hundred R&D projects are instituting more flexible organizational structures, and delegating more decision-making authority to the heads of the various therapeutic areas (Dorey, 2001; Mathieu, 2007).

Beyond economies to scale, biopharmaceutical firms may engage in mergers to gain a presence in an emerging therapeutic category that represents significant future growth opportunities. For example, the oncology class has been characterized by several new ‘first in class’ drugs in recent years (DiMasi and Grabowski, 2007). The oncology class is now the fastest-growing therapeutic category among all major drug classes. The novel entities in this class have emerged primarily from the biotech sector, utilizing molecular biology techniques (for example, new monoclonal antibody products and other targeted agents). Mergers provide a more expeditious way to enter such high opportunity fields relative to internal expansion. It can take several years or even decades to build the internal scientific capability to enter a new therapeutic area or implement a new research platform in an emerging scientific field. This appears to be an important motivation underlying both acquisitions and alliances of developing biotechnology firms by established pharmaceutical firms.

C Alliances as Substitutes or Complements to Mergers

As discussed in section I, larger firms are also increasingly looking to alliances and partnerships with smaller biotechnology firms as the source of new products. This suggests that scale requirements, at least in the discovery and early stages of the development process, remain modest. At these earlier stages, small research-oriented boutique firms may enjoy a number of advantages relative to their larger rivals. These include the fact that they are closer to cutting edge technology emerging from universities and public-supported basic research, are more willing to take risks on disruptive technologies, and are less bureaucratic in organizational structure (Scherer, 1999). By contrast, larger pharmaceutical and biotechnology firms may have advantages in the more advanced stages of development, where large-scale clinical trial design and regulatory coordination become important. This rationale for R&D specialization based on different comparative advantages in research versus development was advanced by Kenneth Arrow (1983) in a more general model of the R&D process.

While alliances and partnerships are an alternative to mergers as a means to acquire new technological platforms and R&D pipeline candidates, they
also pose their own set of issues. Arora et al. (2001) find support for gains from a division of labor at alternative stages of the R&D process. There are also positive network effects associated with alliances and partnerships (Pammolli and Riccaboni, 2004; Powell et al., 1996). On the other hand, partnership deals may be susceptible to a ‘lemons’ problem arising from agency and information problems (Akerlof, 1970; Pisano, 1997). Partnerships also raise challenging bargaining, management and governance issues (Teece, 1998; Arora et al., 2001).

Many mergers and acquisitions in the pharmaceutical area have occurred between firms that had first engaged in some type of alliance or partnership (Higgins and Rodriguez, 2006). This may help merging firms overcome pitfalls associated with agency problems and information asymmetries. In particular, the information gathered over time from an alliance may allow the acquiring firm better to assess the value of the acquired firm’s intangible capital. It may also provide information on the resulting organization’s ability to integrate the strengths of the two companies successfully. The difficulty of integrating firms with different cultures and organizational structures is an oft-cited reason for failures in mergers in the management literature (Larsson and Finkelstein, 1999; Smith and Quella, 1995; Haspeslagh and Jemison, 1991). There is at least some preliminary evidence consistent with these hypothesized benefits from alliances. Higgins and Rodriguez (2006), for example, find that acquisitions involving alliance partners had higher abnormal stock market returns than other pharmaceutical acquisitions. This study is discussed further below, in terms of assessing effects on R&D performance.

**D Increasing Market Share and Antitrust Considerations**

A traditional economic motive for mergers, of course, can be to increase market share and market power to gain competitive advantage. This has not been a major issue in the case of the large pharmaceutical mergers depicted in Table 11.1. In the United States and elsewhere mergers are subject to scrutiny prior to their implementation by the antitrust authorities (Mueller, 1996). There are well-known Department of Justice guidelines on what economic parameters can trigger challenges. In the case of pharmaceuticals, markets are defined in terms of therapeutic categories, since a drug product to alleviate pain, for example, does not compete with one that is approved by the Food and Drug Administration (FDA) for hypertension. Horizontal mergers of significant consequence, therefore, must go through a vetting process before implementation. These negotiations can result in a settlement where competitive products in the
same therapeutic category are spun off as a condition for allowing the merger.

Nevertheless, one of the distinctive areas of antitrust concerns for R&D-intensive pharmaceutical firms is in the area of innovation markets. In particular, this issue arises when two merging parties have potentially competing drug candidates in their R&D pipelines. The concern is that this merger could result in the combined firms suppressing one of the research paths in order to avoid cannibalizing the economic performance with the candidate that is carried forward. The idea that antitrust authorities should concentrate on these dynamic effects of mergers on R&D activities or innovation markets was first advanced in a paper in the economics literature by Gilbert and Sunshine (1995). To date, there have been ten challenges for mergers in innovation markets, and eight of these challenges have involved the pharmaceutical industry (Carrier, 2008).

While the innovation market concept in antitrust enforcement has its supporters, its applications have been criticized by many economists and lawyers (Carlton, 1995; Rapp, 1995; Carrier, 2008). For pharmaceuticals, with their long and uncertain development process, critics argue that antitrust authorities should focus on drug candidates in the late stage of development where potential competition is more easily assessed. Early stage development activities involve relatively low costs and barriers to entry, and are also subject to high levels of uncertainty. Many firms take a portfolio approach to obtaining new product introductions at the early stages of R&D. There are also typically many parallel R&D efforts across firms searching for promising new therapeutic approaches (DiMasi and Pacquette, 2004). When a drug progresses to the final phase III of clinical testing, however, the probability of success increases to approximately 70 per cent, while costs of clinical trials also increase significantly. Traditional anti-competitive concerns about potential competition effects then become more relevant, particularly when there are a small number of late stage competitors for these product candidates.

Carrier (2008) has done an analysis of each of the eight innovative market cases in pharmaceuticals. He finds that some of the challenges by the antitrust authorities are warranted, but others are more problematic given the relevant characteristics of the market and an analysis of the potential costs and benefits. In the questionable cases, he argues that the Federal Trade Commission (FTC) has attempted to protect innovation where future outcomes are uncertain and many years away from the market. By contrast, the EU has taken a less stringent approach to some of these innovation market cases (Morgan, 2001). This is clearly an evolving area of antitrust policy that warrants more research and attention by scholars.
III THE EFFECTS OF PHARMACEUTICAL Mergers AND Alliances ON R&D AND INNOVATION

To date, there have only been a handful of studies that have examined the specific effects of mergers or alliances on innovative activity and R&D productivity in pharmaceuticals. As discussed below, the results are mixed in nature and raise a number of issues and questions for further research.

A Mergers and Acquisitions

Danzon et al. (2007) look directly at the effect of mergers in pharma/biotech on various measures of performance. They focus on mergers with $500 million or more of market value. They find that these mergers are frequently a response to distress, so it is important to compare outcomes for merging firms to outcomes for other firms with similar characteristics, and they create propensity scores for this purpose. They conclude that mergers result in slower growth and a reduction in operating profit, though these effects are rather small. They also find smaller R&D growth for small merging firms. This doesn't speak to productivity directly, and they only look at performance in the first three years following a merger.

Ornaghi (2006) also looks at post-merger performance in the industry, but focuses on productivity. He does not use the propensity score or economic distress index for developing a 'control group' with which to compare the performance of merging firms. He finds that in the three years following a merger, there is a decline in R&D spending as well as productivity, as measured by patents. Koenig and Mezick (2004) focus on a relatively small number of high-profile mergers consummated between 1989 and 1996 (a sample of seven large mergers). Comparing the performance of companies in the industry that undertook these mergers with a control group of firms that didn't, they find that companies that merged were able to achieve more favorable post-merger productivity scores.

To summarize, although prior studies by Henderson and Cockburn (1996), Cockburn and Henderson (2001) and Danzon et al. (2005) generally find some advantage to R&D scale and scope, the studies analyzing merger effects find a weakly negative effect on R&D performance. This may be because there is no additional advantage to size at the level for most mergers, and/or because mergers are a response to distress, in which case the counterfactual is hard to determine. These studies also leave open many questions for further research. First, none of them look at the long-run impact of mergers on a firm's productivity. Three years is unlikely to be enough time to pick up many changes in patenting activity, much less pro-
gression through the phases of development. Second, as Cockburn notes, patents and new chemical entities are not necessarily the best measure of output, though almost all the evidence on productivity centers on these two measures. Third, the focus is on the larger mergers between public firms, and there is little attention paid to heterogeneity in outcomes. The management and finance literatures are concerned with what drives a successful merger, such as whether the R&D activities of merging firms are substitutes or complements, similarities in culture or corporate structure, the integration process, and other economic and organizational characteristics (Hitt et al., 2001). These issues remain important questions for future research.

B  Alliances

The most extensive published study evaluating the performance of alliances has been done by Danzon et al. (2005). They examine the productivity at each phase of drug development (that is, success probabilities) for 900 firms over the period 1988 to 2000. They focus on experience, measured by the number of drugs a firm has in development, rather than sales in looking at economies of scale. They find that the effect of experience on productivity (advancing a drug through a phase) is positive with diminishing returns for phases 2 and 3, with the max occurring at 25 drugs in development. Products developed in an alliance tend to have a higher probability of success, at least for phases 2 and 3 trials, and especially when the licensee is a large firm.

Arora et al. (2007) also examine the role of licensing and alliances in a recent working paper using data from 3000 R&D projects in pre-clinical and clinical trials in the United States in the 1980s and 1990s. After controlling for selection effects, they find licensing improves the probability of success when the licensee is a pharmaceutical firm. Their results are therefore generally consistent with the results of Danzon et al. (2005) on the positive benefits of alliances. Both studies are inconsistent with a ‘lemons’ hypothesis by Pisano (1997), at least for the typical development-oriented licensing arrangement between biotech and advanced pharmaceutical firms.

In contrast to the work on mergers, the studies of alliances find positive effects on R&D performance. These studies indicate that development experience is generally associated with higher success probabilities, especially in later R&D stages. Hence, there appears to be a potentially important role for specialization across R&D stages. An advantage of the studies is that they are performed with R&D project-level data with a large number of observations.
These leading studies on the effects of alliances and innovation, however, also raise many issues for further research. The business alliance literature suggests a rich array of contractual terms and an evolving landscape of ventures. In this regard, Danzon et al. (2005) do not explicitly consider the contractual terms, the extent of integration of the R&D process, or the characteristics of the firms involved in the agreement beyond a few simple attributes relating to a firm’s size and experience in performing clinical trials. Arora et al. (2007) adjust for product selection effects, but their analysis only considers a few characteristic variables. Both studies raise a number of issues about the underlying drivers of successful alliances for further research analysis.

Higgins and Rodriguez (2006) is the only study we are aware of that examines the interactive effects between pharmaceutical alliances and acquisitions. They analyze a sample of 160 pharmaceutical and biotechnology firms engaging in acquisitions between 1994 and 2001. As discussed earlier, with regard to the issue of motivation, they find that firms in economic distress with weak pipeline ‘scores’ and fewer years of (sales weighted) exclusivity for their marketed drugs, were more likely to engage in an acquisition. For the acquisitions involving an alliance partner, they find that the acquiring firms’ pipeline scores improve in the immediate post-merger period. These pipeline scores are based on the count of drugs at each stage of development weighted by the average probability of success for projects at that stage. However, their analysis is short run in nature and only looks at changes in pipeline scores one year post-acquisition. This paper raises interesting issues concerning the long-run interactions between alliances and acquisitions for R&D performance.

IV A NEW RESEARCH STUDY ON THE EFFECT OF MERGERS ON R&D OUTCOMES

A Objectives and Background

In this section we report on some preliminary results from a new research project we recently initiated on the effects of pharmaceutical mergers on R&D outcomes. In contrast to other merger studies, our analysis focuses on the effects at the R&D project level of observation. R&D outcomes are measured in terms of advancement through the various phases of drug research and market launch. It utilizes a large database of more than 4500 firms engaging in pharmaceutical R&D between 1990 and 2007. Our work is therefore closer in character to the research that has been done on alliances. At this point, we report on the data sample and some preliminary
findings regarding research scale effects for merged and non-merged firms in our sample. Eventually, we hope to incorporate information on prior alliances and other firm- and project-level characteristics, including the commercial performance of new product candidates that advance to market launch.

Since data is categorized by stage of development, we give a brief description of the new drug development process here (DiMasi et al., 2003; US Food and Drug Administration, 1999). New drug discovery and development is an information-generating process that passes through well-defined stages. Discovery programs involve the application of basic biomedical knowledge to develop drug candidates for specific disease targets. Pre-clinical testing is then done in assay and animal modules. Clinical (human) testing is typically divided into three basic phases. Phase I involves a small number of healthy volunteers (typically fewer than 100 individuals) to gather information on safe dosages, toxicity and pharmacokinetic effects. Phase II involves testing in patients (usually several hundred) to obtain the initial evidence on safety and efficacy for a drug’s intended indication(s). Phase III tests are designed to establish efficacy, and to uncover less frequent side-effects, with sufficiently large patient populations (usually in the thousands) to satisfy regulatory criteria at accepted levels of statistical significance. The regulatory authorities then review the data and decide whether a drug can be marketed.

The R&D process from a candidate’s synthesis to marketing approval typically takes more than a decade. There is significant attrition at each stage of the process as shown in our analysis below and in other research studies. Project costs also increase substantially for candidates that advance across the different stages of the R&D process. This is driven by the increasing number of subjects and tests that are performed in each successive stage (DiMasi et al., 2003).

B Data on Drug Development Projects

Our primary source for information on drug projects in development comes from IMS R&D Focus. This dataset, typically used by pharmaceutical firms to monitor the research activities of their competitors, provides a history of all projects known to be in development from the mid-1980s to present. This includes projects that failed in clinical trials during this period, those that were successfully launched, and those that are still in development (since projects normally take between 3 and 10 years to complete clinical trials before reaching the market).

Each record in this dataset is a drug project, which can target multiple indications and have multiple firms participating in its development. A
history of the project’s progression through each stage of development is compiled from patent and regulatory filings, presentations at medical conferences, press releases, and information disclosed to financial analysts. Other significant events, including mergers, are also recorded. We identify mergers between private firms using this source, as such mergers would not normally be included in datasets such as SDC Platinum.

When a merger occurs, IMS updates the record of a drug project with the name of the merged firm. In order to examine the performance of a firm prior to a merger, therefore, it is necessary to identify which of the merging firms originated each project that existed prior to the merger. To do so, we rely on patent information (as typically, the patent assignee is the originating firm) as well as the text summary of research for each record. This text summary includes the source of information about a drug’s status; if the source is one of the merging firms, we assume that the project was originated by that source. We can successfully assign about 80 per cent of drug projects that began prior to a merger to one of the merging firms.

Because most of the 4500+ firms in this dataset are not publicly traded in the US, we lack consistent time-series financial data such as R&D spending, total asset size, and other important control variables used in most other studies of mergers in this industry. Those studies focus on the performance of large firms. Our data has the advantage of including firms of varying size, at the cost of poorer information on financial data for non-public firms. To measure firm size, we use the firm’s count of active drug development projects each year, and create 4 size categories: small (fewer than 5 projects underway in a year); medium (5–20 projects); large (20–50 projects); and very large (more than 50 projects).

C Results

We begin by graphing the fraction of projects that advance to the next stage of development by size of firm and by merging firms. Figures 11.2 to 11.4 show the distribution of advancements for phase I–III, respectively (advancement out of phase III means the drug was registered, approved or launched). In each case, the figure includes projects that entered each phase between 1990 and 2003. We assume a five-year window for advancement; this implies some truncation for recent projects (which we observe through the first quarter of 2007), but most projects that advance do so in less than four years.

The effect of size appears to vary across development stages. For drugs in phase I and II, the effects of size on the success probabilities for the firms that did not undergo a merger are relatively small in magnitude. However, there is a strong positive relationship between size and performance in
Source: Authors’ analyses using IMS R&D Focus data.

Figure 11.2 Fraction of projects advanced within 5 years, Phase I to Phase II
Source: Authors' analyses using IMS R&D Focus data.

Figure 11.3  Fraction projects advanced within 5 years, phase II to phase III

Non-merging firms
Merging firms

Size of firm

Fraction of projects

<5 projects  5–20 projects  20–50 projects  >50 projects
Source: Authors' analyses using IMS R&D Focus data.

Figure 11.4 Fraction of projects advanced within 5 years, phase III to launch
phase III. In particular, there is a monotonically increasing relationship and non-merging very large firms launch about 60 per cent more of their phase III projects than small firms.

In all figures, a higher fraction of projects of firms that experienced a merger during the 1985–2006 period progress to the next phase. This leaves open the question of whether high-performing firms are more likely to merge, or whether mergers lead to higher performance. The differences in advancement rates are greater for the smaller firms at each research stage. In addition, the effect of size for merging firms displays a different pattern than that for non-merging firms. However, the most substantial size difference also occurs for phase III. In this final phase, the largest two size classes have distinctly higher probabilities of success than the two smaller classes.

Although we refer to a higher rate of advancement as higher ‘performance’, this is not necessarily true. Because drug development costs increase with each stage, it is better to identify likely failures earlier rather than later. Firms that are better able to make this judgment early on in the development process may advance a lower fraction of projects in phase I or II, but have a higher probability of success for projects that progress to phase III. The higher probabilities of success for phase III for the largest-scale firms are consistent with their comparative advantage at later stages of the R&D process hypothesis (Arora et al., 2001) or alternatively, with the hypothesis that large firms are better at weeding out unlikely successes earlier in the process (Guedj and Scharfstein, 2004). Further research on this issue is warranted.

We next examine the probability that a project advances to the next stage of development within five years, controlling for firm size and the year the project entered its current stage. For projects that entered phase $k$ in year $t$, we estimate a logit regression of:

$$\text{Advance}_k = \beta_0 + \beta_1 \text{Small} + \beta_2 \text{Medium} + \beta_3 \text{Large} + \sum_{t=1990}^{2003} \tau_t (\text{Year} = t) + \varepsilon$$

where small, medium and large correspond to dummy variables for the size categories defined above, and very large size (that is, more than 50 projects) is the omitted category; and $k = 1$ for phase I, 2 for phase II, and 3 for phase III. We estimate a similar regression for each phase including a dummy variable equal to 1 if the project was initiated by a firm that merged after starting the project, and a separate dummy variable equal to 1 if the project was initiated by a firm after merging.

Results are presented in Table 11.2. The coefficients of interest are those on the dummy variables for the size categories and whether the project was
Table 11.2 Logit regression analyses of R&D projects advanced within five years by phase of research, size, and merger experience

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced within five years</td>
<td>Intercept</td>
<td>$-2.14^{**}$</td>
<td>$-1.41^{**}$</td>
</tr>
<tr>
<td></td>
<td>$-2.76^{*}$</td>
<td>$(0.119)$</td>
<td>$(0.140)$</td>
</tr>
<tr>
<td></td>
<td>$-0.06^{*}$</td>
<td>$(0.097)$</td>
<td>$(0.105)$</td>
</tr>
<tr>
<td></td>
<td>$-0.08^{*}$</td>
<td>$(0.089)$</td>
<td>$(0.091)$</td>
</tr>
<tr>
<td></td>
<td>$-0.01^{*}$</td>
<td>$(0.110)$</td>
<td>$(0.116)$</td>
</tr>
<tr>
<td></td>
<td>$-0.05^{*}$</td>
<td>$(0.112)$</td>
<td>$(0.085)$</td>
</tr>
<tr>
<td></td>
<td>$-2.292$</td>
<td>$(0.852)$</td>
<td>$-1.422$</td>
</tr>
<tr>
<td></td>
<td>$2.269$</td>
<td>$(0.852)$</td>
<td>$1.465$</td>
</tr>
<tr>
<td></td>
<td>$3.327$</td>
<td>$(0.852)$</td>
<td>$7.311$</td>
</tr>
<tr>
<td></td>
<td>$1.683$</td>
<td>$(0.852)$</td>
<td>$1.065$</td>
</tr>
<tr>
<td></td>
<td>$1.065$</td>
<td>$(0.852)$</td>
<td>$10.65$</td>
</tr>
<tr>
<td></td>
<td>$58.6$</td>
<td>$(0.852)$</td>
<td>$586$</td>
</tr>
<tr>
<td></td>
<td>Number of observations used</td>
<td>$1065$</td>
<td>$1065$</td>
</tr>
<tr>
<td></td>
<td>Number of projects advanced</td>
<td>$586$</td>
<td>$586$</td>
</tr>
</tbody>
</table>

Note: Year indicator variables corresponding to the year the project entered a particular phase are included but not separately reported.

Source: Authors' analyses using data from IMS R&D Focus.
pre- or post-merger. Year dummies corresponding to the year the project started are also included, but not presented in the table. The table also shows the number of projects analyzed at each stage and the number advanced within five years.5

The pattern of coefficients on the size categories is generally consistent with Table 11.1 and Figures 11.1 and 11.2. Size appears most important, both in terms of the magnitude and statistical significance, for phase III projects. Small and medium-sized firms are significantly less likely to launch their phase III projects relative to large and very large firms. For the earlier development phases, the coefficients on size are usually insignificant and much smaller. When we do not control for projects involved in mergers, smaller firms appear less likely to advance their projects, but the effect of size is non-monotonic.

The second column for each developmental phase considers the effects of mergers. When we include dummy variables for projects that were initiated before or after a merger (the omitted category corresponds to projects of firms that did not merge), the signs of the coefficients on size change, but still are not statistically significant. What is interesting is that projects initiated after a merger are much more likely to advance from each stage of development. This suggests a benefit to merging that is independent of size alone.

An important question for further research is the source of such benefits. Do mergers combine complementary skills of two firms, leading to better project selection? Do mergers reduce potential competition within a disease area, raise expected profits for a project, and therefore lead to more advancement? Are mergers necessary for the realization of these benefits, or could strategic alliances be used instead? Are firms that enter into alliances before mergers more likely to have higher probabilities of success in their R&D projects? These are among the issues we hope to address in future research.

V SUMMARY AND CONCLUDING COMMENTS

As is the case in other industries, mergers in pharmaceuticals are driven by a variety of company motives and conditions. Given this is the case, it is important to take account of firm characteristics and motivations in evaluating merger performance rather than using a broad aggregate brushstroke. Research to date on pharmaceuticals suggests considerable variations and heterogeneity of outcomes.

The empirical research on mergers is generally focused on the larger public companies. There is evidence that the mergers involving these pharmaceutical firms were driven in significant part by a series of industry-wide
and firm-specific shocks. These shocks left many firms with an R&D pipeline gap associated with patent expirations and the increased leverage of payors during the 1980s and 1990s. While these mergers apparently have achieved cost reductions and addressed short-run pipeline problems, there is little evidence to date that they increased long-term R&D performance or outcomes. Many of the larger pharmaceutical firms listed in Table 11.1 continue to deal with a persistent R&D productivity problem.

By contrast, the empirical research on alliances between smaller biotech firms and larger pharmaceutical entities is more encouraging in nature. There is evidence of a positive relation between a firm’s experience in clinical development and the probability of successful outcomes. This suggests a role for small and large firm specialization at different R&D stages. In particular, the ‘R&D boutique’ firms with a small number of research projects can apparently benefit from alliances with larger, more experienced firms, especially at the later stages of the R&D process. The work on alliances provides some support for this hypothesis but also raises a number of issues for further research.

Our preliminary analysis of the effect of mergers on R&D project advancement stages is generally consistent with these results from the alliance literature. In particular, using data on R&D projects from a large sample of public and private firms, we find that a company’s development experience is significantly related to the likelihood of success, especially for the large pivotal phase III trials. Moreover, there is suggestive evidence that very small firms with only a few projects in their R&D portfolio can gain the most benefits from mergers with more experienced firms in developing new drug introductions.

Our results, and those of other studies, are subject to various qualifications and raise many questions for further research. The economic literature indicates, for example, that many acquisitions of smaller companies by larger firms are preceded in time by development stage partnerships. This opens a fruitful line of research in terms of when alliances are a desirable alternative to mergers, and where they can be complementary in nature. More generally, there are a host of interesting research questions to be addressed relating to the various drivers of mergers and the conditions and firm characteristics that produce successful versus unsuccessful mergers. These are important issues from both a business strategy and economic efficiency standpoint. We plan to address some of these questions in our future research agenda by augmenting our large R&D project database with other informational sources.

From an antitrust policy standpoint, the larger horizontal mergers in pharmaceuticals have run into few challenges by the regulatory authorities in the United States and the European Union, given the option to spin off
competing therapeutic products to other drug firms. However, the issue of innovation markets, where firms have potentially competing development programs at very early stages of the R&D process, remains a more controversial area of antitrust policy for industries like pharmaceuticals. This remains an important area for future research by law and economics scholars.

NOTES

1. The sales of a second major biotech firm, Genentech, are included in Roche’s sales in 1999 and 2004, since Roche acquired a majority equity interest in Genentech in 1990. Under the agreement, Genentech has operated as a free-standing company in the United States, with options on foreign licensing rights going to Roche on several of Genentech’s products. The two companies recently signed a joint development, co-licensing option agreement that is currently being implemented for new drug product candidates.

2. The United States is the only major market without some form of price and utilization controls, but also has the largest generic drug market of any country. Generic drug products in the United States now account for more than half of all dispensed prescriptions. (Grabowski, 2007)

3. Based on the R&D Focus database from IMS, the top five companies in Table 11.1 in the latest ranking averaged more than 250 projects across the various stages of the R&D process in 2006.

4. More than 75 per cent of the drugs entering phase I fail to reach the market for safety, efficacy or competitive reasons (DiMasi et al., 2003).

5. As in other studies of success rates, the lowest success rate is at phase II when the first tests of safety and efficacy in patients are performed (DiMasi et al., 2003).

REFERENCES


Mergers and alliances in pharmaceuticals


Koenig, Michael and Elizabeth Mezick (2004), ‘Impact of mergers and acquisitions on research productivity within the pharmaceutical industry’, *Scientometrics*, 59(1), 157–69.


